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Claims

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula I:

$$O = X$$

$$X$$

$$R^{4}$$

$$R^{3}$$

$$R^{3}$$

$$R^{2}$$

Formula I

wherein:

 R^1 is COR^5 or $B(OR)_2$, wherein R^5 is selected from the group consisting of: H, OH, OR^8 , NR^9R^{10} , CF_3 , C_2F_5 , C_3F_7 , CF_2R^6 , R^6 , and COR^7 with R^7 being H, OH, OR^8 , CHR^9R^{10} , or NR^9R^{10} , wherein R^6 , R^8 , R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$,

- CH(R¹)CONHCH(R²)R', CH(R¹)CONHCH(R²)CONHCH(R³)COO R¹¹, CH(R¹)CONHCH(R²)CONHCH(R³)CONR¹²R¹³, wherein R¹, R², R³, R', R¹¹, R¹², and R¹³ are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;
- 20 Z is O, N, or CH;

X is selected from the group consisting of: C=O, C=S and (CRR')_p; p is a number from 1-6;

G is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, alkyl-aryl and alky-heteroaryl with the proviso that G may be additionally optionally and chemically-suitably substituted with U¹¹ or U¹²:

R, R², and R³ may be the same or different and are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8

heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl; R⁴ maybe present or absent, and if R⁴ is present, R⁴ is selected from H, alkyl, aryl; and

Y is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and U, where U is selected from alkyl-aryl, aryl-heteroaryl, alkyl-heteroaryl, alkylcarbonyl, arylalkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, alkyloxycarbonyl, alkyl-aryloxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl, cycloalkyloxycarbonyl, heteroaryloxycarbonyl, heterocycloalkyloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl-arylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, arylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylsulfonyl, cycloalkylsulfonyl, and heterocycloalkylsulfonyl with the proviso that U may be additionally optionally and chemically-suitably substituted with U¹¹ or U¹²; where

U¹¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that U¹¹ may be additionally optionally substituted with U¹²; and

U¹² is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from U¹²; and that said moiety:

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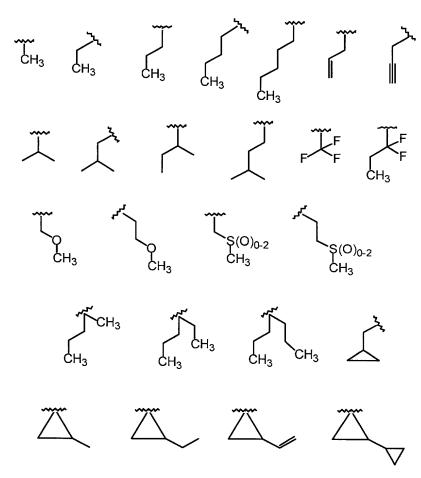
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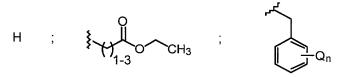
may alternately represent an arylalkyloxy group;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term

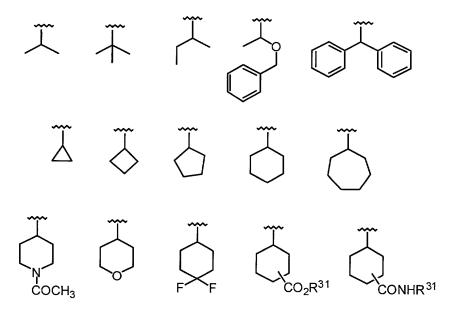
- "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.
- 10 2. The compound of claim 1, wherein R¹ is COR⁵, and R⁵ is H, OH, COOR⁸, and CONR⁹R¹⁰.
 - 3. The compound of claim 2, wherein R^1 is $COCONR^9R^{10}$, and is R^9 is H, and R^{10} is H, CH_2 - $CH=CH_2$, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{2'})$, or $CH(R^{1'})CONHCH(R^{2'})(R^{1'})$.
 - $CH(R^*)CONHCH(R^*)(R^*).$
 - 4. The compound of claim 3, wherein R^{10} is CH_2 -CH= CH_2 .
 - 5. The compound of claim 3, wherein R¹⁰ is CH(R^{1'})COOR¹¹.
 - 6. The compound of claim 5, wherein R^{1'} is H and R¹¹ is H, allyl or benzyl.
 - 7. The compound of claim 3, wherein R¹⁰ is CH(R¹)CONHCH(R²)COOR¹¹,
- 20 CH(R¹)CONHCH(R²) CONR¹²R¹³, or CH(R¹) CONHCH(R²)(R'), wherein R¹ is H and R² is phenyl, substituted phenyl, heteroatom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl and pyridyl.
 - 8. The compound of claim 3, wherein R¹⁰ is selected from the group consisting of CH₂CONHCH(Ph)COOH, CH₂CONHCH(Ph)CONH₂,
- 25 CH₂CONHCH(Ph)CONMe₂ and CH₂CONHCH(Ph)COO-benzyl.
 - 9. The compound of claim 1, wherein R² is selected from the group consisting of the following moieties:



10. The compound of claim 1, wherein G is selected from the group consisting of:



- wherein n is a number from 0-2 and Q is selected from the group consisting of Cl, Br, methyl, methoxy, tert-butyl and combinations thereof.
 - 11. The compound of claim 1, wherein X is C=O.
 - 12. The compound of claim 1, wherein R³ is selected from the group consisting of:



wherein $R^{31} = H$, alkyl or aryl.

13. The compound of claim 1, wherein said moiety:

represents an arylalkyloxy group.

- 14. The compound of claim 13, wherein said arylalkyloxy group is benzyloxy.
- 15. The compound of claim 1, wherein Z is N and R^4 is H.
- 16. The compound of claim 1, wherein Y is selected from the group consisting of H, acetyl, or alkoxycarbonyl.
 - 17. A compound, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula II:

$$V = \begin{pmatrix} G & & & \\ & &$$

Formula II

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wherein:

t is a number from 1 to 3; and when t is 2 or 3, the P moieties may be the same or different;

P is represented by:

wherein V is selected from the group consisting of the following:

wherein R³¹ is independently selected from H, alkyl or aryl;

R¹ is COR⁵ or B(OR)₂, wherein R⁵ is selected from the group consisting of: H, OH, OR⁸, NR⁹R¹⁰, CF₃, C₂F₅, C₃F₇, CF₂R⁶, R⁶, and COR⁷ with R⁷ being H, OH, OR⁸, CHR⁹R¹⁰, or NR⁹R¹⁰, wherein R⁶, R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, CH(R1')COOR11, CH(R1')CONR12R13, CH(R1')CONHCH(R2')COO R11, CH(R1')CONHCH(R2')CONR12R13, CH(R1')CONHCH(R2')R', CH(R1')CONHCH(R2')CONHCH(R3')COO R11

15 CH(R1')CONHCH(R2')CONHCH(R3')CONR12R13, wherein R1', R2', R3', R1, R11, R12, and R¹³ are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is O, N, or CH;

- X is selected from the group consisting of: C=O, C=S and (CRR')_p;
 p is a number from 1-6;
 G is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, alkyl-aryl and alky-heteroaryl with the proviso that G may be additionally optionally and chemically-suitably substituted with U¹¹ or U¹²;
- 10 R, R², and R³ may be the same or different and are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl; R⁴ maybe present or absent, and if R⁴ is present, R⁴ is selected from H, alkyl, aryl; and
- Y is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, and U, where U is selected from alkyl-aryl, aryl-heteroaryl, alkyl-heteroaryl, alkylcarbonyl, arylalkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, cycloalkylcarbonyl, alkyloxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl,
- heteroaryloxycarbonyl, heterocycloalkyloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkyl-arylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, alkylsulfonyl, arylsulfonyl, alkyl-arylsulfonyl, arylalkylsulfonyl, heteroarylsulfonyl,
- cycloalkylsulfonyl, and heterocycloalkylsulfonyl with the proviso that U may be additionally optionally and chemically-suitably substituted with U¹¹ or U¹²; where

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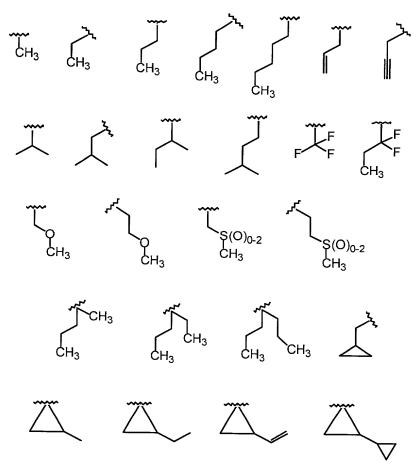
U¹¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that U¹¹ may be additionally optionally substituted with U12; and

U¹² is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from U¹²;

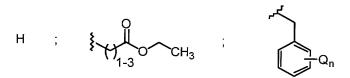
with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

- The compound of claim 17, wherein R¹ is COR⁵, and R⁵ is H, OH, COOR⁸, 18. CONR⁹R¹⁰.
- The compound of claim 18, wherein R¹ is COCONR⁹R¹⁰, and is R⁹ is H, 20 19. and R¹⁰ is H. CH₂-CH=CH₂, CH(R^{1'})COOR¹¹, CH(R^{1'}) CONR¹²R¹³, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or CH(R1')CONHCH(R2')(R').
 - The compound of claim 19, wherein R¹⁰ is CH₂-CH=CH₂. 20.
- The compound of claim 19, wherein R¹⁰ is CH(R¹)COOR¹¹. 21. 25
 - The compound of claim 21, wherein R^{1'} is H and R¹¹ is H, allyl or benzyl. 22.
 - The compound of claim 19, wherein R¹⁰ is CH(R^{1'})CONHCH(R^{2'})COOR¹¹, 23. CH(R1')CONHCH(R2') CONR12R13, or CH(R1')CONHCH(R2')(R'), wherein R1' is H and R2' is phenyl, substituted phenyl, heteroatom-substituted phenyl, thiophenyl,
- cyclohexyl, cyclopentyl, cyclopropyl, piperidyl and pyridyl. 30

- 24. The compound of claim 19, wherein R¹⁰ is selected from the group consisting of CH₂CONHCH(Ph)COOH, CH₂CONHCH(Ph)CONH₂, CH₂CONHCH(Ph)CONMe₂ and CH₂CONHCH(Ph)CO-O-benzyl.
- 25. The compound of claim 17, wherein R² is selected from the group consisting of the following moieties:

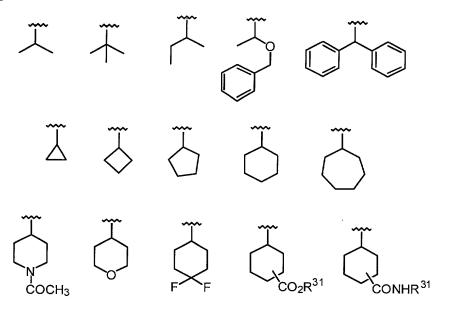


26. The compound of claim 17, wherein G is selected from the group consisting of:



- wherein n is a number from 0-2 and Q is selected from the group consisting of Cl, Br, methyl, methoxy, tert-butyl and combinations thereof.
 - 27. The compound of claim 17, wherein X is C=O.

28. The compound of claim 17, wherein R³ is selected from the group consisting of:



- wherein $R^{31} = H$, alkyl or aryl
 - 29. The compound of claim 17, wherein Z is N and R⁴ is H.
 - 30. The compound of claim 17, wherein P is a peptide moiety selected from $Glu(O^tBu)$ - $Glu(O^tBu)$ -Val and Glu-Glu-Val.
- 31. The compound of claim 17, wherein P is an amino acid moiety selected from Val, Glu(O^tBu) and Glu.
 - 32. The compound of claim 17, wherein t is 1.
 - 33. The compound of claim 17, wherein t is 3.
 - 34. The compound of claim 17, wherein Y is selected from the group consisting of H, acyl, or alkoxycarbonyl.
- 15 35. The compound of claim 34, wherein the acyl group is acetyl group.
 - 36. A pharmaceutical composition comprising as an active ingredient a compound of claim 1 or claim 17.
 - 37. The pharmaceutical composition of claim 36 for use in treating disorders associated with HCV.
- 20 38. The pharmaceutical composition of claim 36 additionally comprising a pharmaceutically acceptable carrier.

- 39. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of claim 1 or claim 17.
- 5 40. The method of claim 39, wherein said administration is subcutaneous.
 - 41. The use of a compound of claim 1 or claim 17 for the manufacture of a medicament to treat disorders associated with the HCV protease.
 - 42. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV protease, said method comprising bringing into intimate contact a compound of claim 1 or claim 17 and a pharmaceutically acceptable carrier.
 - 43. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

Compound	X ²	
9	Boc-Val- (isomer 1)	
10	Boc-Val- (isomer 2)	
11	Ac-Glu(O ^t Bu)-Glu(O ^t Bu)-Val-	
12	Ac-Glu-Glu-Val-	
13	Вос	
14	Н	

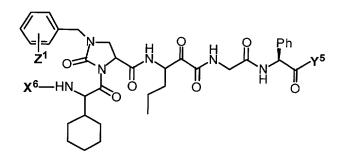
Compound	X^3

15	Boc-Val-	
16	Val-	
17	Ac-Glu(O ^t Bu)-Glu(O ^t Bu)-Val-	
18	Ac-Glu-Glu-Val-	

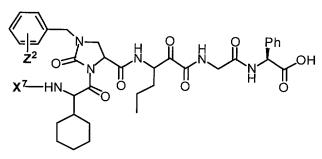
Compound	X ⁴	Y ¹
19	Boc-	allyl
20	Н	allyl
21	Boc-Val-	allyl
22	Ac-Glu(O ^t Bu)-Glu(O ^t Bu)-Val-	allyl
23	Ac-Glu-Glu-Val-	allyl
24	Boc-Val-	Н
25	Ac-Glu(O ^t Bu)-Glu(O ^t Bu)-Val-	Н

$$\begin{array}{c} C \\ C \\ X^5 \\ HN \\ P_3 \end{array}$$

Compound	X ⁵	Y ²	P_3
26	Boc-Val-	allyl	iPr
27	Ac-Glu(O ^t Bu)-Glu(O ^t Bu)-Val-	allyl	iPr
28	Ac-Glu-Glu-Val-		iPr
29	Вос-	benzyl	Chx



Compound	X _e	Z ¹	Y ⁵
30	Вос-	3,4-dichloro	-NH ₂
31	Вос-	4-Bromo	-OBn
32	Вос-	3-Bromo	-OBn
33	Boc-	4-Chloro	-OBn
34	Вос-	3-Chloro	-OBn
35	iBoc-	3,4-dichloro	-NH ₂
36	iBoc-	4-Bromo	-OBn
37	iBoc-	3-Bromo	-OBn
38	iBoc-	4-Chloro	-OBn
39	iBoc-	3-Chloro	-OBn
40	Boc-	4-Bromo	-OH
41	Boc-	3-Bromo	-OH
42	Boc-	4-Chloro	-OH
43	Boc-	3-Chloro	-OH
44	iBoc-	4-Bromo	-OH
45	iBoc-	3-Bromo	-OH
46	iBoc-	4-Chloro	-OH
47	iBoc-	3-Chloro	-OH



Compound	X ⁷	Z^2	
48	iBoc-	Н	
49	Ac-Val-	Н	
50	iBoc-	3,4-dimethyl	
51	Ac-Val-	3,4-dimethyl	
52	iBoc-	3-methyl	
53	Ac-Val-	3-methyl	
54	Ac-Val-	4-methyl	
55	Ac-Val-	3-methoxy	
56	Ac-Val-	4-methoxy	
57	Ac-Val-	4- ^t -butyl	

- 44. A pharmaceutical composition for treating disorders associated with the HCV protease, said composition comprising therapeutically effective amount of one or more compounds in claim 43 and a pharmaceutically acceptable carrier.
- 45. The pharmaceutical composition of claim 44, additionally containing an antiviral agent.
- 46. The pharmaceutical composition of claim 44 or claim 45, still additionally containing an interferon.
- 10 47. The pharmaceutical composition of claim 46, wherein said antiviral agent is ribavirin and said interferon is α -interferon.